Washington

24302/STAN-62-1 3/16/89

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Date: 2/27/89 By: Joy Day

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	
Sherie L. Morrison, et al.	Examiner: Marks, M.
Serial No. 090,669	Art Unit: 185
Filed: August 28, 1987	
For: CHIMERIC RECEPTORS BY DNA SPLICING AND EXPRESSION	AMENDMENT
	Palo Alto, CA 94306

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Office Action of November 29, 1988, please make the following amendments.

IN THE CLAIMS:

Claim 25, line 4, change "promoter" to --transcriptional initiation regulatory sequence--.

Claim 28, line 1, after "having" insert --different--.

Claim 30, line 2, change "hsot" to --host--.

Cancel Claims 1 to 13 without prejudice to renewal.

REMARKS

In view of the above amendments and following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 14 to 38, the only claims under consideration.

Applicants elect Group II without traverse.

The non-elected claims have been cancelled.

Rejections under 35 USC 112 are in part avoided and in part traversed.

So far as the different kinds of receptors, the Examiner has ignored the many limitations on the nature of the claimed receptor coming within the scope of the present claims. First, the receptor must have a variable N-terminal binding region. Second, the receptor must have a non-binding constant region. The receptors the Examiner cites would not have the limitations required by the subject claims, particularly not having variable regions. In each case, the receptor for the proteins which the Examiner cites would have a constant binding region.

Proteins which fit the subject claims are immunoglobulins, the T-cell receptors, and the major histocompatibility complex antigens. Since it is believed that all of these proteins are members of the same supergene family which evolved from a progenitor gene to the various different polymorphic proteins, it is submitted that they share a common nexus, and applicants having shown that one of this group can be prepared as a chimeric product, applicants should be permitted to claim the class generally. Applicants show a number of examples of different immunoglobulins, where each of the products is shown to be effective in binding its complementary hapten.

The rejection of Claims 14, 28, 33 and 36 is respectfully traversed for the reasons given above. The Examiner has apparently not given the weight to the term "variable" which should be given in the subject claims, which distinguishes the subject compositions from the receptors indicated by the Examiner. So far as a multi-unit receptor, it is believed that applicants have indicated that the multi-unit receptor is characterized by having an N-terminal polymorphic region, which provides for a variable amino acid composition for members of the class. Furthermore, there is a constant region, which as Claim 1 indicates, provides for maintaining the structure of the binding region. It is believed with this explanation and the previous discussion, applicants have indicated that their multi-unit

receptor has at least two units, immunoglobulins have four, has a number of members of a family which share structural similarities, and have a polymorphic region which allows for binding to different molecules.

Claim 28 has been amended as suggested by the Examiner, but the Examiner's comment is believed to be inappropriate to Claim 33, since one construct is concerned with a light chain and the other construct concerned with a heavy chain, so they must be inherently different.

The rejection of Claims 25 to 27 for being of improper dependent form is respectfully traversed. It has always been believed that where Claim 1 claims components A and B, a claim dependent on Claim 1 which claims components A, B and C is a narrower claim limiting Claim 1. Since Claim 1 does not require element C, Claim 1 is broader since it may be combined with D, E or F or be by itself. Thus, it is believed that one may add an additional element to a construct which is a plurality of elements. The Examiner is therefore respectfully requested to withdraw this rejection.

Rejection of Claims 14 to 34 and 36 as being anticipated by Cabilly is particularly disturbing. Office Actions are legend which reject claims on the basis that molecular biology is highly unpredictable and, therefore, extrapolations from an event must have clear and certain support in the literature. In fact, the subject Office Action is exemplary of that situation, where applicants have clearly demonstrated immunoglobulins, but the Examiner has rejected the extrapolation for other members of the same supergene family. Thus, gathering together of the literature and cut and pasting various procedures is not considered the equivalent of carrying out the experimentation. Particularly as here, where it could not have been predicted that the structural portion of an immunoglobulin of one species would suffice to maintain the variable region in the proper conformation for specific binding. Thus, the use of paper exemplification in the field of molecular biology should be roundly condemned where there is a significant departure from known experience and one

merely goes to Maniatis, et al., "A laboratory manual" and selects various procedures whereby various known DNA sequences may be restricted, ligated, modified by in vitro mutagenesis or the like to obtain a sequence which has no certainty of being useful.

The paper exemplification of Cabilly is particularly heinous, where the much simpler situation of expressing the naturally occurring heavy and light chains is not shown to be particularly successful.

The Examiner's attention is directed to the table in Cabilly European patent or in the paper on page 2376, the tables being the same. An assumption is made that the amount of protein produced in the cells is 25 µg/ml. Based on the binding affinity, without giving stringency or the nature of the wash, 3.5% of the expected protein is the maximum yield obtained. Secondly, if one looks as to how the antibodies were prepared, the Examiner's attention is again directed to the paper, which is believed to have the same disclosure as the patent. It should be noted that no antibody was obtained when the two subunits were produced in the same cell. On page 2375 is indicated the manner of reconstitution, where the heavy and light chains are denatured and S-sulfonates formed. For reconstitution, the S-sulfonate derivatives are combined with reduced glutathione and allowed to stand in the presence of a number of other components. After dialysis, a resulting product is assayed for CEA-specific binding activity.

The Examiner is requested to show where Cabilly has proven that they have an antibody. All they have shown is that they have a product as a result of combining S-sulfonate derivatives in a buffered medium with a reductant and a composition is obtained which is not analyzed as to structure, molecular weight, or number of subunits, but which is shown to have some binding affinity to its alleged antigen. Thus, all that Cabilly shows is that one can get some specificity from a mixture of subunits which have been joined together by sulfur bonds, where there are a large number of sulfur bonds per subunit, and this mixture will

bind to antiserum specific for the heavy and light chains. This was the sum total of what was obtained where there was no manipulation of the DNA sequences which encoded the natural heavy and light chains, as required by the subject invention.

Yes, Cabilly in the article and Cabilly in the European patent both suggest that it would be useful to try to obtain a chimeric antibody. In fact, in the European application, substantial detail is given as to how one might direct a scientist to carry out experiments to determine whether such a chimera could be obtained in useful form. The difficulties encountered by the applicants where the disclosure is primarily directed to success is evident. The Examiner's attention is directed to page 20, lines 7ff, where only 10% of the transfected cell lines produce both chimeric and light chain polypeptides. Furthermore, it should be noted that the cell lines used by applicants were myeloma cell lines, which would be expected to have the machinery necessary to express and properly process the immunoglobulins. By contrast, Cabilly uses E. coli where proper processing and folding equipment is not available and in fact teaches that one must try to reconstitute the antibodies, that the individual subunits do not combine to form a useful product in the host cell.

If paper disclosures are to be given the benefit of the date of filing, where there can be no certainty of success, then the field of molecular biology will seriously suffer. While one could hope for success by combining a constant and a variable region from two different sources, there could be no certainty. Particularly, where the results like Cabilly are clearly suggestive that with further work, one might be able to obtain a useful product.

Finally, it is noted that the publication date of the Cabilly European patent is November 14, 1984. Applicants parent application was filed in August, 1984. It is submitted that since Applicants have the benefit of their earlier application, the Cabilly European patent until issued in the United States with its priority date of April 1983 is not a reference against

the subject application. However, the Cabilly article clearly is prior to the effective date of the subject application. But for the reasons given above, Applicants do not choose to swear back of the Cabilly article, since it clearly only suggests the possibility of chimeric antibody, without going to the trouble of putting together a paper protocol.

For all of the above reasons, the Examiner is respectfully requested to withdraw the rejection.

Rejection of Claims 35, 37 and 38 under 35 USC 103 based on Cabilly, European patent is respectfully traversed for the above reasons as well as the additional reason that it is not seen why it would be obvious to use myeloma cells, where Cabilly used E. coli cells. Applicants' attorney would certainly wish to agree with the Examiner that this cell line might be obvious to try, but besides the fact that myeloma cells should have the necessary factors for producing immunoglobulins, quite clearly from the experimental section of the subject application, this was not enough. Therefore, the use of myeloma cells is not obvious. Nevertheless, Applicants need not rely upon use of the myeloma cells for patentability, since Applicants believe that the subject invention is patentable regardless of the cell line used.

The combination of Cabilly and Gillies can also be traversed based on the arguments indicated above. It is also noted, that two of the co-authors of the Gillies reference are co-inventors of the subject application. I should say at this time, that the combination of Applicants' constructs and the cells to produce the chimeric immunoglobulins is believed to be novel and patentable and the Examiner is respectfully requested to withdraw this rejection.

In view of the above amendments and remarks, the application is considered in good and proper form for allowance, and the Examiner is respectfully requested to withdraw the rejections and pass this application to issue.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (415) 324-8999.

Respectfully submitted,

LEYDIG, VOIT & MAYER

Date: February 27, 1989

By: _____
Bertram I. Rowland, Ph.D.
Reg. No. 20,015

BIR:slb/jad
PTO:24302

24302/STAN-62-1

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For: CHIMERIC RECEPTORS BY DNA SPLICING AND EXPRESSION

Examiner: Marks, M.

Art Unit: 185

TRANSMITTAL

Palo Alto, California 94306

COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Sir:

Transmitted herewith is an Amendment in the above-identified Application.

[ ] Small entity status of this Application under 37 CFR 1.9 and 1.27 has been established by a Verified Declaration previously submitted.

[ ] A Verified Declaration of Small Entity Status Under 37 CFR 1.9 and 1.27 is enclosed.

[ ] The fee for a -month extension of time is enclosed.

[ ] The fees have been calculated as shown on the next page:

Claims	Remain after Amend.		Highest No. Prev Paid	Pres. Extra	Small Entity Rate	Small Entity Fee	Large Entity Rate	Large Entity Fee
Total:		-		=	x $6 =		x $12 =	
Indep.:		-		=	x $17 =		x $34 =	
If new Mult. Dep. Claims, add					+ $55 =		+ $110 =	

Total Additional Claims Fee:
Extension of Time Fee:
Other: _____:

TOTAL FEES:

[ ] Please charge Deposit Account No. 12-1216 in the amount of the total fees calculated above.

[ ] A check in the amount of the total fees calculated above is attached.

[X] No fee is required.

[X] Conditional Petition for Extension of Time: An extension of time is requested to provide for timely filng if an extension of time is still required after all papers filed with this transmittal have been considered.

[X] The Commissioner is hereby authorized to charge any underpayment of the following fees associated with this communication, including any necessary fees for extension of time, or credit any overpayment to Deposit Account No. 12-1216

[X] Any filing fees under 37 CFR 1.16 for the presentation of extra claims.

[X] Any patent application processing fees under 37 CFR 1.17.

A duplicate copy of this sheet is attached for accounting purposes.

Respectfully submitted,
LEYDIG, VOIT & MAYER

Date: February 27, 1989

By: _____
Bertram I. Rowland, Ph.D.
Reg. No. 20,015

350 Cambridge Avenue, Suite 200
Palo Alto, CA 94306
(415) 324-8999

BIR:jad
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